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Discussion: Session 5* Epidemiologic Investigation of Special Groups

Dr. David Parkinson (University of Pittsburgh and International Steelworkers Union) opened the discussion by reading a letter to a member of the Steelworkers Union from his employer, stating that the worker's employment had been terminated because "extensive testing conducted by our [the company's] physicians has indicated that you [the worker] have unusual propensity to absorb certain amounts of lead in your bloodstream and tissues." The letter went on to state that the worker had a greater response of blood lead than other workers with similar exposures, and because temporary removal from the work environment was not a permanent solution to the problem, the company was terminating his employment. Yet two months previously the worker had been notified that his exposure to lead had been to 21,224 $\mu g/m^3$, way above the current 8-hr standard of 100 $\mu g/m^3$; thus the worker's elevated blood lead had a clear basis from excessive exposure, and was not simply a propensity to absorb more. Dr. Parkinson therefore questioned the value of research on hypersusceptibility to environmental agents. He thought that this meeting showed that epidemiology could not help in providing clean conditions in the workplace, and that perhaps the money spent on epidemiological research would be better spent in preventive measures to protect workers before they are irreparably damaged.

Dr. Hunt replied that we are all concerned about these issues, but made a distinction between the conduct of research and the implications arising from that research. Dr. Radford added that the drop in the bucket that is represented in dollars by the cost of all of the epidemiological research in this country would not clean up ten plants. He thought the issue of allocation of financial resources was a lot broader than was subsumed by the subject of this symposium. He did not think that diverting money away from research would really help; in fact it would bring to a halt investigation of a great number of other materials that may be affecting people, but about which we know very little, in contrast to lead. With regard to differences in susceptibility, from the research standpoint he had a question for Dr. Redmond, also germane to Dr. Murphy's comments about binomialization. We must begin to think of exposure populations as having a continuum of susceptibility and his question was whether a continuum of susceptibility modifies dose-response curves at the low-dose end, and, if so, in what way?

Dr. Redmond replied that a continuous distribution of susceptibilities could affect dose-response relationships, but without any evidence it would be difficult to predict in what way, precisely. If various subsets of the population under study had different dose-response curves characterized by different slopes, indicating some subgroups are more susceptible than others, the total dose response could indeed be affected. Dr. Radford continued by pointing out that in using epidemiologic data for regulatory purposes, one is making the assumption that the population studied is characteristic of the population at large and, therefore, the data are applicable to the general population. But if the conditions of the study population are likely to eliminate susceptible subsets, one might postulate that any dose-response curve obtained in such a study population could underestimate risk very significantly at the low-dose end of the curve. A lot of statements are made that linear extrapolations

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overestimate risk at low doses, but it could be just the opposite. Dr. Redmond agreed that whether or not the study population contains the susceptibles, extrapolations to a general population may very well lead to nonconservative estimates of risk for susceptible subpopulations.

Dr. Charles Land (National Cancer Institute) commented that if there are identifiable and substantial susceptible subpopulations that have a much steeper dose-response curve and for whom the effects might even saturate at low-dose levels, one could get a superlinear dose-response curve. The problem was that he did not know how to analyze data with that kind of general hypothesis. The dose-response relationship that you hypothesize provides the basis whereby data from people exposed to high doses tell you something about risks in people exposed to low doses. If you assume that there is some sort of distribution of extra-sensitive people, the study may have lost all structure, and one is therefore reduced to studying risk at low doses by studying people exposed to low doses. He thought that there is no future in such studies. Dr. Redmond agreed that in terms of biological assay, attempting to define susceptibility in a population survey violated all of the tenets of good statistical design. She did not know a good way to deal with the problem by statistical approaches, either.

Dr. Bernard Altshuler (New York University) said that one would have to use scientific ingenuity. Statistical analysis alone would not suffice. He asked Dr. Redmond whether she thought it was possible to identify susceptible subgroups. Is it feasible for the epidemiologist to try to identify in these studies subgroups which then can be examined, perhaps in other studies? The question is not just to identify the subgroup, but to identify the criteria for characterizing the special susceptibility of a subgroup in advance. Dr. Redmond replied that in many instances it was not, in that some of the factors that one may have to consider as predisposing factors are not clearly delineated. Moreover, such isolation of special groups at risk gets into methodological issues statistically that have not been resolved at the present time. The study may answer major questions about a heterogeneous or mixed study population, but may be limited with regard to sorting out population subsets.

Dr. Hunt pointed out that the immature organism quite likely responds to environmental exposure in a way different from the mature organism. She had been quite surprised to find that it was very difficult to retrieve from any of the Medline literature search systems any designation of juvenile, immature or adolescent individual, be it animal or human. Her concern stemmed in part from the problem of exposure of 10 and 11-year old children to pesticides in their workplace, namely, hand-harvesting of short-term crops. Whether one was concerned with immune responses or reproductive effects, the body burden of a biologically accumulating pollutant was not something to be ignored at these ages. For example, between the ages of 9 to 12, both the testes and the ovaries doubled or tripled in weight; thus the developing child could be at special risk from mutagens. She thought it was time, both in laboratory animals and in epidemiologic studies, to look more closely at the early part of the lifespan.

Dr. Radford said in response to Dr. Land's comments that he wanted to dispel the rather hopeless implication about detecting low-dose effects. One of the important results of this symposium has been that epidemiologists who are going to be dealing with these problems have become aware of the great number of new tools that can help to identify special populations at risk and begin to get a quantitative assessment of how important they are in determining low-dose effects. About ten different promising susceptible subsets that need to be looked at as special cases in terms of reactions to environmental agents have already been identified at this meeting alone. He thought that studying low-dose effects is anything but hopeless. That is the challenge that now faces epidemiologic research: to begin to identify and study these groups so that we can make much better sense out of low-dose effects of a variety of environmental agents. Dr. Land replied that he was talking about the possibility there may be unidentified subgroups, and the difficulties in this case. If one can identify them in advance then you have something.

Dr. Redmond said that her remarks were aimed at putting the issues into perspective. As one who is by training primarily a statistician, she felt that she had to rely heavily on biologists as to what are the biological mechanisms of disease and to know what factors to build into studies and study design. These concepts are important in elucidating whether or not there may be susceptible subpopulations. Once data have been collected, attempting to pull out groups that are somewhat deviant from the total population raises important questions about the appropriateness of such a procedure. Dr. Altshuler agreed that the really critical issue is whether the investigator can identify the special group in advance or not. Dr. Philip Enterline (University of Pittsburgh) commented that we should not lose sight of something obvious:

that there are characteristics of individuals which make them susceptible that epidemiologists can identify very easily. An obvious example is cigarette smokers exposed to asbestos, a subset of the population which is susceptible to lung cancer. Another characteristic is age, as Dr. Hunt mentioned. There could be characteristics of residence, or people with hobbies may have unusual exposures. He thought these are things that should be addressed in more of our studies.

Dr. William A. McClellan (Gulf Science and Technology Company) addressed a question to Dr. Redmond or Dr. Murphy about the appropriateness of extrapolating results from radiation effects at low-dosage to the effects of chemicals at low-dosage, which may differ for many reasons. Dr. Redmond replied that she had not meant to imply that results from one kind of an exposure, whether it be radiation, polycyclic hydrocarbons or whatever, could be applied to another situation where you are dealing with different materials and different responses. Decisions about appropriate dose-response relationships have to be made based upon what is known about the biology of the material, and what seems reasonable from previous experience. One should not take information from one totally different setting and apply it to another.

Dr. Murphy began by denying the major premise. As he had listened to the series of questions asked, he thought that the assumption that the way to look at an environmental factor and its results is in terms of a dose-response curve at low doses, was not at all obvious. For example, for a man exposed to lead, could one not measure his exposure and measure his blood lead level? This approach does not get into problems of bionomialization or any particular problems of low dosage. It may be that the level of lead in the blood is only an intermediate stage between the environmental hazard and what one is really interested in. Despite such objections, if one does not use an empirical dose-response curve but instead uses regression analysis, then he thought this should be expressly addressed. This alternative is possibly related to the comment about using science: rather than using a black-box treatment of a relatively crude outcome, to use a relatively refined regression variable in analyzing results. He also commented that if one is talking about taking money away from the study of genetics, why don't we go whole hog and put most funding into the study of moral philosophy?

Dr. J. Wanless Southwick (Utah State Department of Health) asked: If we recognize that environmental quality is a continuum of "dosage levels" over time and space, rather than simply a binomial bad or good quality, and if we construe a standard to be something of a dividing line between acceptable and unacceptable exposures, and if we further assume that somewhere in the general population there are individuals who make up a subset of susceptibles that may be difficult or even impossible to identify, how then do we set standards? Specifically, how do we re-evaluate standards that have already been set based on limited data? Do we set more stringent standards for well-known and unpopular pollutants? Is there an inevitable vested interest struggle between the producer of the pollutant, who wants to minimize costs, and the regulator, who wants to maintain the public image of an unyielding champion of public health? In short, his question was: Do epidemiologists and their findings actually have much to do with the standard-setting process?

Dr. Hunt replied that for those who have had front-line experience of having to deal with what was either inadequate or poor quality epidemiologic studies in the standard setting exercise, the process was difficult. She had watched with sympathy her colleagues struggle with this problem, knowing that there would be criticism of a study, not necessarily because of the quality of the work the epidemiologist did, but because the reality of a study population was not as good as if one studied rats in the laboratory instead. She commented on the case of the Alsea study, in which a decision was made not to set a standard but to issue a regulatory decision concerning the exposure of human populations to 2,4,5-T and its contaminant, dioxin. The experience is interesting to recount, because the media event the Alsea study became made it quite reasonable to everybody watching the scene, whether scientists or the general public, that the subsequent decision made by the Environmental Protection Agency to suspend that herbicide for a large number of uses was made on the basis of those Alsea findings. In fact, in the decision process that went on, the Alsea study was simply a trigger to a re-evaluation of the animal toxicology for 2,4,5-T and dioxin. It was decided that the appropriate, prudent public health practice was to take action on the basis of the animal toxicology, when there was suspicion of human effect. The decision was not based on the inadequate epidemiology. EPA looks upon the 2,4,5-T dioxin issue as a serious concern. The scientific foundations that go into decision-making involve not just one component, but many lines of evidence that are interactive. Those who have the final decision do take account of many sources of scientific evidence, no matter what some scientists think and the media present to the public.

Dr. Robert Chapman (EPA, Research Triangle Park, North Carolina) said that he had not been involved directly in the standard-setting process, but in the first phases of the standard-setting process, at least for the ozone standard with which he had worked, epidemiology figured quite prominently. There had been a very reassuring kind of interaction between the regulators and the epidemiologists at EPA in North Carolina. As the author of the epidemiology chapter in the criteria document for ozone and photochemical oxidant, he had been consulted frequently by people in the Office of Air Quality Planning and Standards as to the reasonableness of things they were writing. They consulted him more than he sometimes wanted, but he had no hesitation in saying they were extremely conscientious in wanting not to wander too far afield of what was reasonable in terms of available data, especially epidemiologic data, and the evidence of significant biomedical effects. The OAQPS finally defined a range of about 0.08 to 0.12 ppm hourly average, within which the photochemical oxidant standard might be reasonably set, and within which it was difficult to give priority of one value over another from the available biomedical evidence. In his view in this case, at least, the standard-setting process definitely did take account of epidemiologic evidence.

Dr. Parkinson stated that his experience had been a totally different one. He had been chief of the Occupational Health Branch in California for a couple of years, and was involved in standard setting there. Because of limited resources, one had to set priorities for the sort of substances that should be aggressively regulated. He never found that he could use epidemiologic results to set priorities. The priorities were, unfortunately, set by many factors. One has to recognize that what happens in that sort of pressure cooker, whether it is a state health department or the federal Occupational Safety and Health Administration, is that priorities are influenced by pressures which are not based upon science or upon epidemiology. The OSHA regulations demonstrate this fact. In the 23 standards set since the initial promulgation of the Act, he could not think of any of the 23 where a conscious decision had been made that those 23 were the important substances for which standards should be set. Secondly, in none of the 23 could he think of an instance where epidemiologic data were used to initiate the standard-setting process. The pressures to regulate came largely from unions, chiefly from the Oil, Chemical and Atomic Workers and the Steelworkers unions. At the public hearings involved in the regulatory process to set a standard, a lot of epidemiologic evidence was brought forward that really should have been used to initiate the proceedings in the first place. Animal data were usually ignored. They just do not get considered in the way they should be. From his experience with the standard setting process, science does not play a great part in where the standard is set. For example, in the cases of kepone, DVCP or asbestos, he did not think epidemiologic data were really the relevant issue. The conflicting pressures between the unions, on one side, wanting standards set, and industry, on the other side, wanting the standard to be feasible from an economic point of view, were the major determinants in setting standards for those substances.

Dr. Martin Hines (Division of Health Services, State of North Carolina) said that the cotton dust standard of OSHA was set almost exclusively on the basis of epidemiologic studies done by the State Health Department in North Carolina. He had been discouraged by a great lack of concern about occupational disease by organized unions and labor. While his group had struggled to do this epidemiologic study in the textile mills, he did not get any encouragement from labor unions to help with it. Unions may be very interested in the final standard, but when the real work was being done to define health risks they were not there. Dr. Parkinson replied that if anyone tried to do anything about occupational health in a nonunion shop, people lose their jobs. Therefore, you cannot study or prevent occupational disease in an unorganized workforce in North America because people just get fired, and they disappear and are never seen again.

Dr. Radford asked Dr. Kline, were the dose-response curves that she showed fitted *a priori*, or were they fitted to the data itself? He had noticed she did not show any data points on her graphs and he was concerned whether in fact one could just as well have drawn any of the variety of dose-response curves that we had heard about earlier in this symposium. Dr. Kline replied they were not fitted *a priori*. As far as the abortion data go, the curves were fitted by using maximum likelihood logistic regression. Before Kline et al. had started thinking about dose-response curves for this conference, they had analyzed the smoking data in three categories: nonsmokers, women who smoked up to 13 cigarettes, and women who smoked from 14 to 80 cigarettes. From these data, they suspected that the curve should be S-shaped, and plateau after about 20 cigarettes. The curves which were fit, fit very well; the value for the χ^2 between the observed and expected values was on the order of 0.50, but there are a number of curves

that might have fit. The smoking data were not fit well by a linear curve, which was the first curve they attempted. The poor fit was owed not to effects at the low doses, but to effects at high doses where there was a definite plateau. There is no question that women who were smoking 40 cigarettes a day did not show effects where a linear curve would predict. A quadratic component was added to the linear term and this component was significant. However, they did not think such a curve made biological sense because eventually it would turn down and then smoking would become protective. They turned then to the logarithmic curve which fit the data at the full range of doses studied. This function has the advantage that it plateaus at the higher doses. A threshold model also gave a good fit at low doses; indeed there was not sufficient power to distinguish between a threshold and logarithmic model at low doses (1-4 cigarettes).

Dr. Hunt stated that we have all watched with interest development of data on the relationship of smoking to the high risk of early abortion, yet with normal chromosome complement. She asked Dr. Kline whether the same situation holds for alcohol. Dr. Kline replied that results for alcohol are a bit more complicated. There is definitely an association between alcohol and abortion of chromosomally normal conceptions. When she spoke of chromosomally normal fetuses in relation to smoking, she was talking specifically about well-formed fetuses. A lot of abortions seen are empty sacs and growth-disorganized embryos. These are instances where development is stopped very early in gestation. Once you have a well-formed fetus, development has progressed at least beyond 10 weeks. With excess alcohol intake by the mother, association is with abortion of chromosomally normal conceptions of all sorts, but they also have found a strange unexplained association with the abortion of nontrisomic chromosomally abnormal conceptions. In the data last analyzed, the numbers were really too small to distinguish the type of aneuploidy which may be associated with alcohol drinking. The numbers are probably just about big enough to go back and see if they can replicate the association of alcohol drinking with aneuploidy and also to study which chromosomal anomalies, if any, are associated with drinking. Since nearly all anomalies arise before or during conception, an effect would have to be ascribed to drinking before conception. There is, of course, overlap in women who drink frequently prior to conception and during pregnancy.

Dr. Hunt commented that perhaps the data base now being developed with these methods can be used for evaluating the effect of exposure of women to toxic substances—either during pregnancy or prior to conception—for example, investigation of effects of fat-soluble organic compounds. She asked Dr. Kline from her experience whether we are at the stage where we can use these results as preliminary data or whether there will be limitations in using worker populations.

Dr. Kline responded that they have been thinking about this problem because, of course, it is enormously difficult to collect a series of abortions, so that if one could take their series and those of others and use these as comparison groups, a good deal of time and money would be saved. As far as the chromosomal anomalies go, their series of abortions and some of the other series probably provide useful comparison groups. Although they have a good deal of information on independent variables which may need control (e.g., smoking, alcohol use), many series of karyotyped abortions do not include this information, and thus there are limitations to the use of these data. Of the five or six series of karyotyped spontaneous abortions, there are many similarities and also some interesting dissimilarities. But there are more similarities than dissimilarities and once one knows the gestational state of the pregnancy and the maternal age, estimates of the frequency and type of anomaly across studies are similar, suggesting that adjustment for these factors may be sufficient for some comparisons.

Their data are probably not very useful for prediction of rates of spontaneous abortion, partly because of study design. Although they have set out rates for spontaneous abortions using all abortions and live births coming to the study hospitals, they are not able to define precisely for these two different reproductive outcomes the cohort of women who use these hospitals. If one wanted to examine whether the rate of abortion was raised in a factory, for instance, it might be difficult to locate an appropriate comparison group. In the literature there are several series where abortion rates are given for a cohort of pregnancies, and these may sometimes provide a rather gross test of whether the rate of abortion appears raised in a particular setting.

Dr. Hunt asked whether data comparable internationally and across racial groups had been found. Dr. Kline stated they had not yet found what they thought was a racial difference in their studies. Jacobs has a series in Hawaii which is even more diverse with respect to race than their New York population, and she does not find any racial variation. In New York there is an unexplained association of socioeconomic status with triploidy in their

series. Among the private patients, that is the women of high socioeconomic level, there is an excess of triploidy, a particular kind of chromosomal anomaly. Interestingly enough, this is one of the anomalies which varies most between studies across the world. The association seems to be with social class rather than with race; however, it is difficult to disentangle race and social class because the private patients are nearly all white and public patients are not.

Barbara Hays (University of Pittsburgh) spoke as an environmentalist who had attended the conference just to listen. Much of this symposium on environmental epidemiology has dealt with the problem of how you use epidemiology for standard setting. She thought the conferees had lost sight of the fact that people concerned with the environmental quality are talking, for example, about clean air or clean water. They are not worried simply about whether materials in water or air are going to give us cancer or an excess of miscarriages or something like that. As Dr. Radford had said earlier, we should be aware of the perceptions of people about their environment, and what they perceive as a safe or pleasant environment. Somehow we need to learn how to quantitate these perceptions, because these really represent people's goals. She had the feeling that the emphasis on health is primarily because of the ways laws are written. Perhaps that is because the only way to achieve environmental quality is by moving entrenched economic interests to change the way they do things, and this can only be done by emphasis on health effects such as production of cancer or miscarriages. But somehow we need to be able to get at some of these perceptions of people, that don't have such long-term endpoints, like cancer. She hoped there would be some way of quantifying the behavioral effects on people, such as headaches or more frequent illnesses, and relating those to environmental degradation.

Dr. Nurtan A. Esmen (University of Pittsburgh) was bothered by her comments because perception of the environment is very subjective. When W. C. Fields was living he objected to very clean water; he liked his water contaminated with alcohol. What one person perceives as clean and what someone else perceives as clean may be completely different. We have to try to define what clean is. Somewhere one must make some sort of tests, some epidemiological study of these effects. The endpoint could be some index of perception. Dr. Jeff Beaubier (EPA, Research Triangle Park) commented that in parts of the world where there is low per capita income but still a high life expectancy, in such places perhaps these qualities of the environment have contributed to longevity. For example, villages in Greece or Sweden have very good qualities of environment, and possibly therefore higher life expectancy.

Dr. Hunt summed up by pointing out that we have brought together at this symposium an integration of the imperfections of the real world and attempts to reach perfection in epidemiologic studies. The fact is that we have a responsibility to get as good answers as we can to the effects of the environment on people, while well aware that we have a wide range of variation in people to deal with.